

### **Remarks**

This paper is in response to the Office Action dated January 26, 2007 rejecting pending claims 1-19 over the prior art. Applicants amendments to the claims in response to the Final Office action dated January 9, 2007 have not been entered by the Examiner. The Examiner has asserted that the limitations drawn to a loss in the electrodes ability to measure current is new requiring further consideration and/or search. Furthermore, the Examiner has asserted that the molecules such as the L- and D-forms of cystine and homocysteine that can be used to coat the electrode (amended claim 64), are also new and require further consideration. Applicants request continued examination of the instant application, and believe that the amended claims represent patentable subject matter.

### ***Amendments to the Claims***

Claim 1 has been amended to recite a coated metal electrode wherein the coating does not result in a loss of the electrochemical properties of the electrode. Additionally, the coating is selected from a group consisting of 2-mercaptoethanol, 2-mercaptoethylamine, thiophene, L-cysteine, L-cystine, D-cysteine, D-cystine, L-homocysteine, D-homocysteine, and helps to increase the temporal stability of the coated electrode as compared to an uncoated electrode. Support for this amendment can be found in the specification, particularly on page 3, lines 28 and 32, as well in Table 1 and in Table 2 of the specification as filed. Claims 18 and 19 have also been amended to further incorporate the limitations of claim 1. In addition, claims 1, 18 and 19 have been amended to overcome the Examiner's § 112 rejection. Finally, Applicants have cancelled claims 2-13. Applicants have also added new claim 20-23 that depend on amended claim 18, and new claims 24-27 that depend on amended claim 19. The subject matter of new claims 20-23 and 24-27 is the same as that of pending claims 14-17. Applicants request the Examiner to enter the amendments and believe that all pending claims are now in condition for allowance and allowance is therefore respectfully requested.

### ***Claim Rejections under 35 USC § 112***

Claims 1-19 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter the applicant regards as the

invention. Particularly, the Examiner states that the limitation requiring the coating to “not result in a loss of the desired sensing characteristics of the electrode” is vague and confusing.

Applicants have amended the claim language to overcome the Examiner’s rejection, and clearly define the claimed invention. Claim 1, as amended, now recites a coated metal electrode wherein the coating does not result in a loss of the electrochemical properties of the electrode. Claims 18 and 19 have also been amended to incorporate this limitation. Applicant’s believe that the amended claims are now in condition for allowance, and allowance is therefore requested.

***Claim Rejections under 35 USC § 102(b)***

*Rejection over French:*

Claims 1, 2, 18, and 19 are rejected by the Examiner under 35 USC § 102(b) as being anticipated by French et. al., (Langmuir, 3-19, 1998, 2129-2133). Applicants respectfully disagree. Furthermore, claim 2 has been cancelled, and claims 1, 18 and 19 are pending.

Amended claim 1, recites a coated metal electrode, wherein the coating comprises a sulfur containing moiety in its molecular structure. Additionally, the coating does not result in a loss of the electrochemical properties of the electrode, e.g., the electrode’s ability to pass current. Amended claim 1, further recites that the coating is selected from a group consisting of 2-mercaptoethanol, 2-mercaptoethylamine, thiophene, L-cysteine, L-cystine, D-cysteine, D-cystine, L-homocysteine, D-homocysteine, and results in a coated metal electrode whose temporal stability is greater than a temporal stability of a corresponding uncoated metal electrode.

The French reference pertains to the enhancement of the barrier properties of alkane-thiol coated gold electrodes using 1-octanol as a surfactant. Particularly, French differs from the instant invention in at least two ways. First, the emphasis in French is on the capacity of alkane thiol monolayers to inhibit the oxidation of the underlying gold electrode, as well as the oxidation of redox-active species via direct interaction with the electrode. French also discloses the improvements in barrier properties of alkanethiol coated electrodes when over layered with a surfactant such as 1-octanol. According to French, the thiol-surfactant layer reduces the surface

oxidation of the underlying gold electrode by preventing contaminants and/or redox active solutes from depositing on to the surface of the electrode. In fact, French explicitly discloses that the octanol-thiol layer inhibits the oxidation of a gold electrode in pH 5.0 buffer, at applied potentials between 0V and +1.6V versus a silver/silver chloride reference electrode. Thus, the absence of gold oxidation and gold oxide reduction at applied potentials where these reactions would readily be observed using an uncoated gold electrode indicates that the thiol-surfactant layer together generate a barrier on the electrode that is completely free of defects that would allow the direct contact of gold surface with an electrolyte solution (page 2130, col. 2, para 2 and Figure 1). In another embodiment, French demonstrates the effectiveness of the alkane thiol-surfactant layer as a barrier in preventing the oxidation of ferrocyanide in solution. As disclosed by French, the thiol coated electrode acts as a barrier to ferrocyanide oxidation, with a shift in the oxidation-peak from +0.3 V to +1.1 V. The addition of an octanol layer over the thiol layer further shifts the oxidation of ferrocyanide to a more positive potential of 1.6 V. This shift in the oxidation potential of ferrocyanide to more positive potentials is indicative of the formation of a barrier layer on the surface of the gold electrode, *which restricts the ferrocyanide ions from approaching the electrode. This forces the redox reactions to occur via a long-range electron transfer process across the mono-layer* (page 2131, col. 1, para 1; and Figure 2).

A second point of distinction between the French reference and the instant application is the use of long chain alkane thiols for the monolayer on gold electrode by French (octanethiol, decanethiol and dodecanethiols). In contrast, as taught by amended claim 1, the instant invention uses short chain cyclic and acyclic thiols as well as sulfur containing amino acids to coat the electrode surface.

In the instant application, the thiol monolayer serves as a barrier to prevent unwanted hydrophobic contaminants from accumulating on the surface of the electrode without significantly impeding the rate of electron transfer between electrolyte and electrode surface. Stated differently, the short chain thiol layer essentially allows the coated electrode to behave in a manner similar to an uncoated electrode. The thiol layer does not alter the amount of current that passes through a coated electrode in comparison to an uncoated electrode. Additionally, this layer further prevents a loss in the flow of current through the coated electrode as a function of

time and over replicate measurements. Thus the function of the thioalkane barrier in the instant application is to *prevent contaminants from altering the electrochemical behavior of the electrode*. As stated above, French explicitly teaches a barrier that forces electro-active species to undergo oxidation-reduction chemistries over a long-range, viz., across the long chain alkane-thiol barrier.

Thus, the thiols used to coat the electrode surface in the instant application are chemically distinct and serve a different function from the thiols disclosed in French. Amended claim 1, is therefore patentably distinct over French.

Claims 18 and 19 have also been rejected by the Examiner as being anticipated by French. Applicants have amended claims 18 and 19 to incorporate the limitations of amended claim 1 and therefore believe that claims 18 and 19 contain allowable subject matter .

Additionally, new claims 20-23 and 24-27 which depend on amended claims 18 and 19 have been added. Dependent claims 20-23 and 24-27 incorporate all the limitations of their respective base claim and therefore represent allowable subject matter. Furthermore, dependent claims 20-23 and 24-27 independently distinguish over French, since claims 20-23 and 24-27 require using a stereospecific compound or a mixture of the two stereoisomers of a compound to coat the electrode surface. French does not disclose such a coating. Thus claims 18 and 19 as well as the claims that depend on these two independent claims represent allowable subject matter.

*Rejection over Schweiss:*

Claims 1, 2, 6, 7, 10, 11, 18, and 19 are rejected by the Examiner under 35 USC § 102(b) as being anticipated by Schweiss et. al., (Material Science Forum (1998), pp287-288). Claims 2, 6, 7, 10, and 11 have been cancelled. Claims 1, 18 and 19 are currently pending.

The Schweiss reference pertains to the kinetics of adsorption/desorption of various surfactants to/from the surface of a gold electrode coated with a self-assembled monolayer (SAM) of *1-octadecanethiol*. Further, Schweiss discloses the influence of pH and ionic strength

on the capacitance of a gold electrode coated with a monolayer of hydrophilic  $\omega$ -terminated alkylthiols (e.g., 16-mercaptohexadecanoic acid and 20-mercaptoicosylamine). However, Schweiss does not teach the use of short chain thiols to coat the surface of an electrode as disclosed in amended claim 1, nor does this reference disclose a thiol coat that essentially acts as a barrier to prevent unwanted hydrophobic contaminants from adhering to the surface of the electrode. Additionally, Schweiss does not disclose a thiol layer that does not alter the electrochemical properties of the electrode, namely the amount of current that flows through the coated electrode in comparison to an uncoated electrode without a loss in current carrying ability of the coated electrode as a function of time (i.e., coating does not result in a loss of the electrochemical properties of the electrode). Finally, Schweiss fails to disclose improving the temporal stability of the coated electrode as taught by claim 1. Claim 1 is therefore patentable over Schweiss. Dependent claims 14-17 are also patentable over Schweiss since they incorporate all the limitations of amended claim 1. Additionally, claims 14-17 are also separately patentable over Schweiss since the claims recite to the use of stereospecific compound for coating an electrode. Schweiss does not disclose such a coating.

Claims 18, and 19 have been amended by the Applicants to incorporate all the limitations of amended claim 1. Independent claims 18 and 19 are therefore patentable for at least the same reasons mentioned above for amended claim 1. Finally, claims 20-23 and 24-27 are also patentable over Schweiss since they depend on claims 18 and 19 and incorporate the limitations of these base claims. Also, claims 20-23 and 24-27 disclose the use of a stereospecific compound or a mixture of its stereoisomers to coat an electrode surface. Schweiss does not disclose coating electrode surfaces using stereospecific molecules as required by the new claims 20-23 or 24-27. Thus claims 20-23 and 24-27 are patentable over Schweiss. Applicants therefore believe that all pending and new claims are allowable.

*Rejection over Dong:*

The Examiner also rejects claims 1, 2, 18, and 19 under 35 USC § 102(b) as being anticipated by Dong et. al., (Biochemistry and Bioenergetics, 42 (1997), pp 7-13). The Examiner asserts that Dong discloses the use of a lipid as an overcoat on the alkanethiol coated electrode.

Additionally, the Examiner asserts that the lipid overcoat reads on a surfactant and thus teaches the applicants claimed invention. Claim 2 has been cancelled. Applicants respectfully disagree and state that claims 1, 18 and 19 are distinct over the prior art.

First, Dong does not teach or disclose coating an electrode using the short chain alkane thiols disclosed by amended claim 1. As stated above such a coating is desirable as it allows a coated electrode to essentially display electrochemical properties similar to an uncoated electrode i.e., allows for reproducible use over extended periods of time and over multiple analysis without any loss in the electrochemical properties of the coated electrode (namely, the current carried by the coated electrode) when compared to an uncoated electrode under similar conditions of use. The thiol coat further improves the temporal stability of the electrode. Since the Dong reference does not disclose the short chain alkane thiols of amended claim 1, Dong does not anticipate amended claim 1.

Second, although Dong discloses the use of phospholipids to overcoat an alkane thiol coated electrode such an overcoat does not broadly read on the surfactant overcoat disclosed by amended claim 1.

Lipids are fatty acid esters of glycerol and are hydrophobic by nature. This is a fundamental characteristic of lipids. In case of phospholipids as disclosed by Dong, one of the hydroxyl groups of glycerol is esterified using a phosphate group. Thus phospholipids are negatively charged at physiological pH. Triton X-100 (1,1,3,3-tetramethylbutyl phenyl poly(ethyleneglycol ether)<sub>x</sub>, the surfactant used by the instant invention is a non-ionic (i.e., uncharged molecule). In addition, Triton X-100 has a poly ethyleneglycol ether head group that imparts polarity without the charged (ionic) characteristics of phospholipids. This difference allows surfactants to sit at the interface of oil and water with the polar head group in contact with the aqueous phase via hydrogen-bonding. Lipids on the other hand are either non-polar hydrophobic compounds, or can have a charged end (head group) and a hydrophobic tail as in the case of phospholipids. In either case, such charged molecules are unable to effectively sit at the oil-water interface since they cannot undergo effective hydrogen-bonding with water. The net result is that when a phospholipid as disclosed in the Dong reference, is used to fill the

defects in the alkane thiol coat, the lipid will adsorb on to the surface of the electrode via its phosphate group, leaving its long chained hydrophobic tails exposed to water. The hydrophobic tails of the phospholipid will tend to exclude water from the electrode surface. The net result is that the phospholipid overcoat will prevent electrolytes from approaching the electrode surface and therefore prevent and/or hinder the electrochemical reaction occurring at the electrode surface.

In contrast, Triton X-100 with its long polar poly ethyleneoxide ether chain (as head group) will tend to attract water to the electrodes surface, which in turn will promote or enhance the ability of electroactive groups to approach the electrode surface.

Thus amended claim 1, distinguishes over Dong for two reasons:

(1) Dong does not disclose the short chain alkane thiols taught by amended claim 1.

(2) The phospholipid overcoat cannot be used as a substitute for the surfactant taught by amended claim 1, because such a substitution would alter the electrochemical properties of the electrode as mentioned above. Thus amended claim 1, represents patentable subject matter.

Further, the examiner asserts that claim 18 pertaining to a method for coating a metal electrode and claim 19 that teaches a method for sensing an analyte using a coated electrode are unpatentable over Dong. Applicants respectfully disagree.

Claims 18 and 19 have themselves been amended to include all the limitations of claim 1. As discussed above it is not possible to replace the surfactant overcoat by the phospholipid without altering the electrochemical behavior of the electrode. Additionally, Dong teaches the incorporation monensin and/or valinomycin into the lipid coat for detecting monovalent ions (e.g., sodium and potassium) in a sample solution. The instant application does not require the incorporation of either monensin or valinomycin into the surfactant layer for detection of ions. Thus amended claims 18 and 19 are patentable for at least the same reasons mentioned for claim 1.

Finally, the new dependent claims 20-23 and 24-27 are also patentable since they depend on amended claims 18 and 19 respectively. Furthermore, dependent claims 20-23 and 24-27 essentially teach the use of stereospecific thiols as coatings for electrodes. Dong does not disclose such a coating and therefore does not meet the limitation of these claims. Applicants therefore believe that all pending and new claims are allowable.

***Claim Rejections under 35 USC § 103(a)***

Claims 1-7, 10-13, 18, and 19 are rejected by the Examiner under 35 USC § 103(a) as being unpatentable by Allen et. al, in view of French. Claims 2-7 and 10-13 have been cancelled by the Applicants. Independent claims 1, 18 and 19 are currently pending.

The Allen reference discloses coating the surface of electrodes with different sulfur containing compounds to assess their ability to promote direct electrochemistry of cytochrome-c at a gold electrode. However, as stated by the Examiner, Allen does not teach or even suggest the use of a surfactant overcoat let alone the coating of the claims as amended. The Examiner relies on French to teach the use of such an overcoat. Applicants respectfully disagree and state that neither Allen nor French alone, or together, teach the Applicant's claimed invention.

French discloses using long chain alkane thiols to coat an electrode and serve as a barrier to oxidation of the underlying electrode. French further discloses the enhancement of the barrier properties by using a surfactant such as 1-octanol to overcoat and fill the defects in the underlying alkanethiol monolayer. As stated above in response to the Examiner's §102 (b) rejection, French explicitly discloses redox reactions to occur via a long range electron transfer process across the alkane thiol monolayer. Secondly, the French reference does not teach or even mention using the short chain alkane thiols disclosed in amended claim 1.

Allen also does not disclose the thiol compounds of amended claim 1. In fact, this reference teaches the use of surface modifiers and/or promoters to coat metal electrodes used for electrochemical studies with cytochrome-c. In addition, Allen makes no specific reference to using a surfactant to fill defects in the layer coating electrode surface. Since Allen does not remedy the deficiency of French with respect to the type of thiols that can be used to coat an



electrode, Allen in combination with French does not build the Applicants claimed invention. Additionally, combining the surfactant overcoat taught by French with the coated electrode of Allen, still does not result in the Applicants claimed invention. Hence, there one of ordinary skill in the art would not and could not combine Allen with French to build the claimed invention, since neither reference teaches using the particular thiol compounds disclosed in amended claim 1 to coat a metal electrode, and therefore, a combination of these two references would not result in a device having all of the limitations of amended claim 1. Amended Claim 1 is therefore patentable over Allen in view of French.

Independent claims 18 and 19 have been amended to include the limitations of amended claim 1. Claims 18 and 19 are also patentable over Allen in view of French for at least the same reasons mentioned above for claim 1. Furthermore, new dependent claims 20-23 and 24-27 which disclose the use of stereospecific compounds as coatings have been added. First, claims 20-23 and 24-27 are patentable over Allen in view of French since they ultimately depend on claims 18 and 19 respectively, and thus incorporate all of the limitations of the base claims. Additionally, since neither Allen nor French disclose the use of stereospecific compounds as coatings, these references either alone or in combination do not meet all the limitations of claims 20-23 or 24-27. Thus claims 18-27 represent allowable subject matter and allowance is respectfully requested.

The Examiner also rejects claims 1, 2 and 6-19 under 35 USC § 103(a) as being anticipated by Schlereth et. al, in view of French. Claims 2 and 6-13 have been cancelled. Claims 1 and 14-19 are currently pending.

Schlereth teaches methods for preparing and using self assembled mono-layers capable catalyzing the oxidation of NADH in the absence of redox mediators at fairly low anodic overpotentials. To achieve this, Schlereth, uses cysteine and/or cystamine to coat a metal electrode surface in order to support electroactive dyes such as those having a phenothiazine or a phenoxazine ring system. The dyes are covalently conjugated to the surface modified electrodes (SME's; coated electrode surface) by further derivatization of the free amino groups of cysteine or cystamine with a bifunctional reagent that further allows covalent bonding of the

electroactive dyes onto the electrode's surface. This covalent complex of cysteine-bifunctional reagent (linker)-redox dye supported on the electrode surface is used for studying electrochemical oxidation of NADH systems. Thus, Schlereth does not disclose the coating of amended claim 1, nor does he disclose the use of a surfactant to overcoat the electrode as taught by amended claim 1. Furthermore, Schlereth does not teach or suggest improving the temporal stability of the coated electrode and Schlereth additionally does not disclose using the short chain thiols disclosed in amended claim 1. Thus the teachings of this reference are different from those of claim 1 of the instant application. Thus claim 1 is patentable over Schlereth.

Claims 14-17 depend on claim 1 and incorporate all its limitations. Furthermore, claims 14-17 disclose using stereospecific compounds to coat electrodes, and not the conjugate of a stereo-compound with a bifunctional linker as taught by Schlereth. French also does not teach or suggest the use of stereospecific compounds for coatings. Thus claims 14-17 separately distinguish over Schlereth either independently or in combination with French.


Claims 18, and 19 have been amended to further include all the limitations of amended claim 1 and therefore contain patentable subject matter. Furthermore, the new dependent claims 20-23 and 24-27 teach coatings from stereospecific compounds and further incorporate all of the limitations of their independent claims. As mentioned above, French does not disclose the use of stereo analogs as coatings. Although Schlereth discloses using cycteine or cystamine to covalently link redox active dyes to the electrode surface, this reference discloses using the sulfur amino acids in conjunction with bifunctional linker compounds. Thus, the molecules used as coating by Schlereth differ chemically and in function from the chiral compounds mentioned in independent claims 18 or 19. As mentioned above, French also does not disclose the compounds of claims 18 and 19. Hence, all claims are patentable over Schlereth and French either individually or in combination. Allowance is respectfully requested.

### CONCLUSION

Applicants believe that the presently pending claims are in immediate condition for allowance and allowance is therefore respectfully requested. However, should any issues remain, the Examiner is urged to telephone the undersigned Attorney for Applicant in the event that such a communication is deemed to expedite allowance of this application.

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Respectfully submitted,

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